Amendments to the Specification:

At page 1, please amend the paragraph beginning at line 6 as follows:

Pursuant to 35 U.S.C. §371, this is a national stage of International Application No. PCT/US98/25314, filed November 27, 1998 and claiming benefit of U.S. Provisional Application No. 60/066,863, filed November 28, 1997, the entireties of each of which are incorporated by reference herein. ~~This application claims priority to U.S. Provisional Application Serial No. 60/066,863, filed November 28, 1997, which is incorporated by reference herein.~~

At page 5, please amend the paragraph beginning at line 7 as follows:

FIGURE 2. Amino acid sequence and multiple alignment of the PAS domains of MOP1 (SEQ ID NO:10), MOP2 (SEQ ID NO:11), MOP3 (SEQ ID NO:12), MOP4 (SEQ ID NO:13) and MOP5 (SEQ ID NO:14). The amino acid sequence including a CLUSTAL alignment of the bHLH-PAS domains is depicted. The CLUSTAL alignment was performed using the MEGALIGN program (DNASTAR, Madison, WI) with a PAM250 weight table using the following parameters: Ktuple = 1, Gap Penalty = 3, Window = 5. Amino acid boundaries for the residues encompassing the bHLH and PAS domains of the MOPs were defined based on previous observations. The bHLH domain is boxed, while the basic region is specified by a vertical line. The PAS domain is underlined, while the "A" and "B" repeats of the PAS domain are boxed. Consensus (60%) residues in the PAS domain are denoted with an asterisk.

At page 7, please amend the first two paragraphs together, as follows:

FIGURE 5. The consensus DNA binding site for MOP3-MOP4 heterodimer *in vitro*. Ten selected DNA sequences bound by the MOP3-MOP4 complex are indicated with the E-box core boxed (from top to bottom, SEQ ID NOS: 110, 111, 112, 113, 114, 115, 116, 117, 118 and 119). Underneath, the M34 consensus is indicated (SEQ ID NO:120). Nucleotide positions relative to the E-box core are shown. Bases in uppercase are randomer derived, while bases in lower case are primer derived.

FIGURE 6 [[5]]. Interaction panel of LexAbHLH-PAS fusion proteins with full-length MOP3 and ARNT. Fig. 6A [[5A]]: Schematic representation of the LexAbHLHPAS "bait" and the full-length "fish." The bHLH and PAS domains are boxed. The "A" and "B" repeats of the PAS domains are indicated. The transactivation domain of the full-length "fish" is indicated. Fig. 6B [[5B]]: LexA fusion protein plasmids containing the bHLH-PAS domains of HIFlα, HIF2α, MOP3, MOP4, AHR, ARNT, and CLOCK were coexpressed with plasmids harboring full-length MOP3 and ARNT (see Materials and Methods). LexAAHR interactions were assayed on plates containing 1 μM β-naphthoflavone. After incubation, an 5-bromo-4-chloro-3-indolyl 13-β-galactoside overlay assay was performed. ++, A strong interaction, turning blue within 2 hr; +, a weaker interaction, turning blue between 8 hr and overnight; and -, a negative interaction after overnight incubation. The experiment was performed three times with identical results.

~~FIGURE 6. The consensus DNA binding site for MOP3-MOP4 heterodimer *in vitro*. Ten selected DNA sequences bound by the MOP3-MOP4 complex are indicated with the E-box core boxed. Underneath, the M34 consensus is indicated. Nucleotide positions relative to the E-box core are shown. Bases in uppercase are randomer derived, while bases in lower case are primer derived.~~

At page 29, please amend the paragraph beginning at line 20 as follows:

Recombinant systems employing any of MOPs 3, 4, 8 or 9 may be used to screen for drugs that modify circadian rhythms. In connection with this embodiment, as described in greater detail in Example 2, we have determined the binding sequence for the MOP3/MOP4 heterodimer, and have constructed the following recombinant plasmids: PL833, a MOP3 expression vector for mammalian cells; PL834, a MOP4 expression vector for mammalian cells; and PL880, a reporter plasmid (expressing luciferase) driven by the MOP3/MOP4 consensus enhancer sequence GCA_CACGTG_ACC (SEQ ID NO: 124). When the three plasmids are introduced into a mammalian cell, the reporter gene responds to the presence of the MOP3/MOP4 dimer. This system is used in a high throughput microwell assay to screen for compounds that are specific activators or inhibitors of these transcription factors. A similar system has been established for MOP7 (HIF3α), as set forth in Example 3.

At page 31, line 1 through page 32, line 3, please amend the table as follows:

OL21 5' CGAGGTCGACGGTATCG 3' (SEQ ID NO:19)

OL22 5' TCTAGAACTAGTGGATC 3' (SEQ ID NO:20)

OL124 5' CCCAAGCTTACGCGTGGTCTTTGAAGTCAACCTCACC 3' (SEQ ID NO:21)

OL145 5' AGCTCGAAATTAACCCTCACTAAAGG 3' (SEQ ID NO:22)

OL176 5' CGGGATCCTTACACATTGGTGTTGGTACAGATGATGTACTC 3' (SEQ ID NO:23)

OL180 5' GCGTCGACTGATGAGCAGCGGCGCCAACATCACC 3' (SEQ ID NO:24)

OL201 5' GATAAGAATGCGGCCGCAGATCTGGGTCCGAAGCACACG 3' (SEQ ID NO:25)

OL202 5' CATTACTTATCTAGAGCTCG 3' (SEQ ID NO:26)

OL226 5' CGGGATCCTCATGGCGGCGACTACTGCCAACC 3' (SEQ ID NO:27)

OL365 5' GACAGTTGCTTGAGTTTCAACC 3' (SEQ ID NO:28)

OL386 5' TTATGAGCTTGCTCATCAGTTGCC 3' (SEQ ID NO:29)

OL387 5' CCTCACACGCAAATAGCTGATGG 3' (SEQ ID NO:30)

OL392 5' CCGCTCGAGTGATGAGCAGCGGCGCCAACATCACC 3' (SEQ ID NO:31)

OL393 5' CCGCTCGAGTGGCAGCTACAGGAATCCACC 3' (SEQ ID NO:32)

OL404 5' GCGGTACCGGGACCGATTCACCATGGAG 3' (SEQ ID NO:33)

OL414 5' TCGAGCTGGGCAGGGTACGTGGCAAGGC 3' (SEQ ID NO:34)

OL415 5' TCGAGCCTTGCCACGTACCCTGCCCAGC 3' (SEQ ID NO:35)

OL418 5' GTAAAACGACGGCCAGT 3' (SEQ ID NO:36)

OL419 5' GGAAACAGCTATGACCATG 3' (SEQ ID NO:37)

OL443 5' TCGAGCTGGGCAGGGTGCGTGGCAAGGC 3' (SEQ ID NO:38)

OL444 5' TCGAGCCTTGCCACGCACCCTGCCCAGC 3' (SEQ ID NO:39)

OL445 5' TCGAGCTGGGCAGGTCACGTGGCAAGGC 3' (SEQ ID NO:40)

OL446 5' TCGAGCCTTGCCACGTGACCTGCCCAGC 3' (SEQ ID NO:41)

OL447 5' TCGAGCTGGGCAGGTTGCGTGGCAAGGC 3' (SEQ ID NO:42)

OL448 5' TCGAGCCTTGCCACGCAACCTGCCCAGC 3' (SEQ ID NO:43)

OL450 5' TACTGGCCACTTACTACCTGACC 3' (SEQ ID NO:44)

OL456 5' AACCAGAGCCATTTTTGAGACT 3' (SEQ ID NO:45)

OL477 5' GCTCTAGAGGCCACAGCGACAATGACAGC 3' (SEQ ID NO:46)

OL479 5' GATCGGAGGTGTTCTATGAGC 3' (SEQ ID NO:47)

OL489 5' TTAGGATGCAGGTAGTCAAACA 3' (SEQ ID NO:48)

OL496 5' GTTCTCCATGGACCAGACTGA 3' (SEQ ID NO:49)

OL499 5' CGGGTACCCTGGGCCCTACGTGCTGTCTC 3' (SEQ ID NO:50)

OL500 5' CGGCTAGCCTCTGGCCTCCCTCTCCTTGATGA 3' (SEQ ID NO:51)

OL514 5' CTGGGAGCCTGCCTGCCTTCA 3' (SEQ ID NO:52)

OL520 5' CCCAAGGAGAGGCGTGAT 3' (SEQ ID NO:53)

OL540 5' GGGATCCTCGTCGCCACTG 3' (SEQ ID NO:54)

OL541 5' ATGCAGTACCCAGACGGATTTC 3' (SEQ ID NO:55)

OL560 5' TGCACGGTCACCAACAGAG 3' (SEQ ID NO:56)

OL561 5' TTGCCAGTCGCATGATGGA 3' (SEQ ID NO:57)

OL565 5' CTGAACAGCCATCCTTAG 3' (SEQ ID NO:58)

OL568 5' AGCTTGCCCTACGTGCTGTCTCAG 3' (SEQ ID NO:59)

OL569 5' AATTCTGAGACAGCACGTAGGGCA 3' (SEQ ID NO:60)

OL590 5' AGAGGTGCTGCCCAGGTAGAA 3' (SEQ ID NO:61)

OL611 5' CAATGATGAGGGAAACACTG 3' (SEQ ID NO:62)

OL657 5' CGGGATCCCGTCAACTGGAGATGAGCAAGGAG 3' (SEQ ID NO:63)

OL665 5' CTGCAAAAATCCGATGACCTCTT 3' (SEQ ID NO:64)

OL681 5' CGGGCAGCAGCGTCTTC 3' (SEQ ID NO:65)

OL682 5' GCGTCCGCAGCCCCAGTTG 3' (SEQ ID NO:66)

OL683 5' TTCAATGTTCTCATCAAAGAGC 3' (SEQ ID NO:67)

OL684 5' GAACAGTTTTATAGATGAATTGGC 3' (SEQ ID NO:68)

OL689 5' GAGGTGTTTCAATTCATCGTCT 3' (SEQ ID NO:69)

OL715 5' GGGATCCGTGACCGATTCACCATGGAG 3' (SEQ ID NO:70)

OL716 5' CTGCAGGTCACACAACGTAATTCACACA 3' (SEQ ID NO:71)

OL717 5' GGGATCCGTATGACAGCTGACAAGGAG 3' (SEQ ID NO:72)

OL718 5' GGTCGACGTCACAGGACGTAGTTGACACA 3' (SEQ ID NO:73)

OL719 5' GAATCCATGAGCAAGGAGGCCGTG 3' (SEQ ID NO:74)

OL720 5' GGTCGACGTCAAACAACAGTGTTAGTTGA 3' (SEQ ID NO:75)

OL721 5' GGGATGCGTATGGATGAAGATGAGAAAGAC 3' (SEQ ID NO:76)

OL722 5' GGTCGACGCTAGACCGAGTGTGTGCA 3' (SEQ ID NO:77)

At page 53, please amend the paragraph beginning at line 17 as follows:

Reagents. Oligonucleotides were supplied by GIBCO/BRL and designated as follows:
OL522 5'-GACAGTATCACGCCTCTCCTT-3' (SEQ ID NO:78)
OL579 5'-AGCGGCGTCGGGATAAAATGA-3' (SEQ ID NO:79)
OL595 5'-ATGCTGAACTGTGCCGAAAACTGT-3' (SEQ ID NO:80)
OL656 5'-GAACAGTGGGGTGGGTCCTCTTT-3' (SEQ ID NO:81)
OL990 5'-GGAATTCTGAGTCTGAAC-3' (SEQ ID NO:82)
OL991 5'-GGAATTCCACGCTCAGG-3' (SEQ ID NO:83)
OL992 5'-GGAATTCTGAGTCTGAAC(N)13CCTGAGCGTGGATTCC-3' (SEQ ID NO:84)
OL1116 5'GATCGGACACGTGACCATTGGTCACGTGTCCATTGGACACGTGACC-3' (SEQ ID NO:85)
OL1117 5'-GATCGGTCACGTGTCCAATGGACACGTGACCAATGGTCACGTGTCC-3' (SEQ ID NO:86)
OL1155 5'-GATCGGATACGTGACCATTGGTTACGTGTCCATTGGATACGTGACC-3' (SEQ ID NO:87)
OL1156 5'-GATCGOTCACGTATCCAATGGACACGTAACCAATGGTCACGTATCC-3'. (SEQ ID NO:88)

The yeast LexA fusion plasmid pBTM116 was provided by P. Bartel and S. Fields (State University of New York, Stony Brook). The yeast strain L40 was a kind gift of S. Hollenberg (Fred Hutchinson Cancer Research Center, Seattle, WA). The yeast strain AMR70 was constructed by Rolf Sternglanz, and was a kind gift of S. Hollenberg. LexA antiserum was a kind gift of J. W. Little (University of Arizona). pSGBCU11 was a kind gift of Stephen Goff (CIBA-Geigy, Research Triangle Park, NC). Human CLOCK was a kind gift of T. Nagase (Kazusa DNA Research Institute, Chiba, Japan). Mammalian expression vectors were purchased from GIBCO/BRL (pSVSport) and Promega (pTarget). Antibodies specific for MOP3 and MOP4 were prepared against peptides specific for each protein as described (Poland et al., 1991, Mol. Pharmacol. 39:20-26). The MOP3 peptide sequence was DNDQGSSSPSNDEAAC (SEQ ID NO:125) and the MOP4 peptide sequence was KDKGSSLEPRQHFNALDVGC (SEQ ID NO:126).

At page 57, please amend the paragraph beginning at line 14 as follows:

MOP3 and MOP4 Screened Against Known bHLH-PAS Proteins. To confirm the specificity of the MOP3-MOP4 interaction, we reversed the interaction trap strategy and screened full-length MOP3 against all bHLH-PAS proteins available in this laboratory. As a positive control we compared these results to a parallel screen using full-length ARNT. Western blot analysis using anti-LexA sera indicated approximately equal expression levels for all fusions. The full-length MOP3 protein interacted strongly with LexAbHLH-PAS fusions of MOP4, CLOCK, and HIF2α and weakly with HIF1α (Figure 6 [[5]]). No interaction of full-length MOP3 could be detected with LexA fusions of MOP3, AHR, ARNT, or the LexA control. Full-length ARNT demonstrated robust interactions with HIF2α and the AHR, and weaker interactions with HIF1α. We did not detect full-length ARNT interactions with LexAbHLH-PAS fusions of MOP3, MOP4, CLOCK, ARNT, or the LexA control (Figure 6 [[5]]).

At page 58, please amend the paragraph beginning at line 14 as follows:

DNA Binding Specificity of the MOP3-MOP4 Heterodimer. We performed a selection and amplification protocol to identify the DNA sequence bound with high-affinity by the MOP3-MOP4 complex. After three rounds of selection and amplification, a gel shift assay was performed using radiolabeled selected randomers to identify the migration of the complex. We identified a species dependent on the presence of both proteins. A band corresponding to this migration was excised from the polyacrylamide gel, and used as template for a fourth round of amplification before cloning the pool. Analysis of the sequencing data from 10 clones revealed that the MOP3-MOP4 heterodimeric pair bound the sequence G/TGA/GACACGTGACCC (SEQ ID NO:120) (Figure 5 [[6]]). This sequence is an imperfect palindrome containing a core E-box enhancer element (defined as CANNTG, underlined) and specificity for nucleotides in the flanking region (e.g., +4 "A"). We refer to this response element bound by the MOP3-MOP4 as M34. To demonstrate sequence binding specificity and to confirm the selectivity for the +4 nucleotide, we performed competition experiment varying the +4 position to A, C, G, or T (Figure 5 [[6]]). In agreement with our selection results, we observed a strong preference for the flanking +4 "A" nucleotide by the MOP3-MOP4 complex.

At page 59, please amend the paragraph beginning at line 30 (and continuing onto page 60) as follows:

MOP3 Forms Functional DNA Binding Complexes with HIFlα and HIF2α. Prompted by our yeast interaction results, we set out to determine the ability of MOP3 to form DNA binding complexes with HIFlα *in vitro*. Because of the asymmetry at the +4 position of the M34 element, we were uncertain which half-site was bound by MOP3. Therefore, we synthesized enhancer elements with the HIFlα 5' half site (TAC) fused to both of the potential MOP3 3' half-sites described above (GCCCTACGTGACCC, SEQ ID NO:121 or GCCCTACGTGTTCC; SEQ ID NO:122). We found that the HIF1α/MOP3 complex preferred the GCCCTACGTGACCC (SEQ ID NO:123) element *in vitro*, suggesting that MOP3 preferred an "A" at the +4 position. Therefore the corresponding response element bound by the HIF1α-MOP3 complex, which we refer to as M13, was used in subsequent experiments. The results demonstrate that the M13 element is bound in the presence of the MOP3-HlFlα combination, but not by either protein alone. MOP3-specific and HIFlα-specific antisera abolished this complex while preimmune IgG did not. For comparison we included ARNT in these experiments, and found that ARNT-HIFlα band was more intense than the MOP3-HIF1α complex when all proteins were used at equimolar concentrations.

At page 66, please amend the paragraph beginning at line 2 as follows:

Gel-shift oligonucleotides. The complementary oligonucleotide pairs used in gel-shift assays are shown below (5' to 3'). They contain a constant flanking sequence and the wildtype or mutant HRE core sequence (underlined):

OL396 TCGAGCTGGGCAGGTAAGGTGGCAAGGC (SEQ ID NO:89)

OL397 TCGAGCCTTGCCACGTTACCTGCCCAGC (SEQ ID NO:90)

OL398 TCGAGCTGGGCAGGTGAGGTGGCAAGGC (SEQ ID NO:91)

Ol399 TCGAGCCTTGCCACGTCACCTGCCCAGC (SEQ ID NO:92)

OL414 TCGAGCTGGGCAGGGTAGGTGGCAAGGC (SEQ ID NO:93)

OL415 TCGAGCCTTGCCACGTACCCTGCCCAGC (SEQ ID NO:94)

PCR Oligonucletides:

OL1014 GCCATGGCGTTGGGGTGCAG (SEQ ID NO:95)

OL1017 ACTGTGTCCAATGAGCTCCAG (SEQ ID NO:96)

OL1178 GCCTCCATCATGCGCCTCACAATCAGC (SEQ ID NO:97)

OL1210 CCCCGTTACTGCCTGGCCCTTGCTCA (SEQ ID NO:98)

OL1323 AGCCGAGGGGGTCTGCGAGTATGTTGC (SEQ ID NO:99)

OL1324 GCTGCTGACCCTCGCCGTTTCTGTAGT (SEQ ID NO:100)

OL1397 GTCGACGCCACCATGGACTGGGACCAAGACAGG (SEQ ID NO:101)

OL1427 GGATCCTCAGTGGGTCTGGCCCAAGCC (SEQ ID NO:102)

OL1548 GCGGGGTGCTGGGAGTGGCTGCTAC (SEQ ID NO:103)

OL1698 GCCTTCCTGCACCCGCCTTCCCTGAG (SEQ ID NO:104)

OL1769 GCGGCCGCAAAAAACAAGACCGTGGAGACA (SEQ ID NO:105)

OL1771 GCCCTGGGAGAATAGCTGTTGGACTTTGGGCAATTGCTCACT (SEQ ID NO:106)

OL1772 GCGGCCGCCTATTCTGAAAAGGGGGGAAA (SEQ ID NO:107)

AP1 CCATCCTAATACGACTCACTATAGGGC (SEQ ID NO:108)

AP2 ACTCACTATAGGGCTCGAGCGGC (SEQ ID NO:109)